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16. ABSTRACT

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The Use of Sensory Evoked Potentials in Toxicology[1,2]

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The Use of Sensory Evoked Potentials in Toxicology. DYER, R. S. (1985). *Fundam. Appl. Toxicol.* **5**, 24–40. The rationale for studying sensory systems as an integral part of neurotoxicological examinations is presented. The role of evoked potentials in assessing brain dysfunction in general and sensory systems in particular is also presented. Four types of sensory evoked potentials (brainstem auditory evoked response, somatosensory evoked potentials, flash evoked potentials, and pattern reversal evoked potentials) are discussed in terms of their demonstrated contributions to neurotoxicology and clinical neurology. Research needed to allow these methods to achieve their full value for neurotoxicology is identified and briefly discussed.
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The type of information needed in neurotoxicology is not substantially different from that needed by other branches of toxicology. Methods must be available which allow screening for potential neurotoxicity, characterizing or defining the parameters of neurotoxicity (e.g., what systems are affected, and in what way), understanding mechanisms of neurotoxicity, and evaluating the health effects of exposure. Physiological studies, and in particular neurophysiological studies, make contact with each of these four needs. This paper discusses a set of neurophysiological methods, referred to as sensory evoked potentials, which have demonstrated particular promise in characterizing neurotoxicity and assessing potential health effects of exposure to toxicants. The starting point for the types of studies to be described is a situation in which a particular compound is suspected to be neurotoxic, but the brain systems affected have not been fully defined. The discussion will (1) address the rationale for assessing sensory systems, (2) discuss the rationale for using evoked potential measures for making the assessments, and (3) provide examples of several specific sensory-evoked potential tests.

WHY INVESTIGATE SENSORY SYSTEMS?

Although it is possible to divide the central nervous system into many smaller functional units and call each of them a system, it is convenient for our purposes to think of all brain function as falling into one of three systems. Sensory systems involve the processing of all information provided to the nervous system by the external environment. Motor systems involve the control of outputs from the nervous system. For lack of a better term, all remaining activity can be thought of as belonging to an integration and maintenance system. Studies of sensory systems have the advantage that the response of the nervous system to a well-defined yet moder-

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ately normal (i.e., physiological) input signal (stimulus) can be evaluated. Precise specification and control of the input stimulus reduces variability in the measured endpoints, and should thereby increase the clarity with which toxicant-induced perturbations may be detected.

In addition to precision in defining the inputs, study of sensory systems affords easy access. In other words, the system can be stimulated in a noninvasive manner. Lights may be flashed and tones presented without the need for surgery, but precisely controlled activation of other systems requires implantation of stimulating electrodes. While it is true that electrodes must be affixed for recording the sensory response to the externally applied stimulus, these must be applied no matter what the stimulus.

Certain neurotoxicants seem to have a particular affinity either for sensory systems in general or for one sensory system in particular. Examples of these apparent special sensitivities will be presented in subequent sections of this paper. In addition, there are few cases for which there is evidence that a nonsensory system is affected, and efforts have failed to reveal concomitant sensory damage. If there are reasons why sensory systems in general are particularly sensitive to neurotoxicants, these reasons are not known. It is important to make clear that no argument is made here that sensory systems should be evaluated to the exclusion of other systems. Rather, the point is that evaluation of sensory systems should rarely if ever be excluded from a group of studies designed to characterize a suspected neurotoxicant.

WHY USE EVOKED POTENTIAL TECHNIQUES?

Once a decision has been made to assess sensory systems using neurophysiological methods, there are still at least three different approaches which may be taken. These are (1) to use macroelectrodes for recording ongoing spontaneous activity (EEG) from these areas, (2) to use microelectrode techniques to study the areas, and (3) to use macroelectrode or evoked potential techniques. The only serious choice is between the latter two approaches. If one were to record the spontaneous activity in the absence of a stimulus, one of the compelling reasons for selecting a sensory system in the first place would have been bypassed. Whether one chooses macroelectrode or microelectrode techniques depends entirely upon the question which the studies are intended to answer. Keeping in mind that the goal of the types of studies described here is to help identify and characterize the systems involved in cases of suspected neurotoxicity, and to evaluate their health effects, evoked potential studies are more desirable than microelectrode studies. To make the rationale for this choice clear, some of the advantages and disadvantages of each approach will be outlined.

Evoked potential techniques generally use macroelectrodes, or large electrodes. Little if any special preparations are required for their successful use, and they are very cheap. In many cases a thin stainless-steel factory-insulated wire is used. For cortical recordings small stainless-steel screws are often threaded into the skull. In human studies small disks are often placed directly on the scalp. The recorded activity represents the integrated postsynaptic activity of the pool of neurons in the vicinity of the electrode. The extent to which the activity of any given cell type is represented in the averaged response to a stimulus is a function of (1) the extent to which there are active inputs to that cell type from the sensory system, and (2) the number of functional cells of that type in the general vicinity of the recording electrode. Note that it is not necessary that a cell produce an action potential to have its activity recorded; it is only necessary to produce a postsynaptic response to an input. The size of the recorded waves of the evoked potential is in part an indirect reflection of the number and size of cells responding to the stimulus.

An often-overlooked advantage of using sensory-evoked potentials in neurotoxicology is that homologous tests may be performed in human and nonhuman studies. Indeed, many of the procedures implemented in the neurotoxicology laboratory were derived from the neurological clinic, where they are becoming routine adjuncts to diagnosis and characterization of certain types of neurological dysfunction (Beck *et al.*, 1975).

While evoked potential techniques provide a valuable window on the functional integrity of the system under study as a whole, it is important to stress that alterations induced in evoked potentials by exposure to toxic substances provide little information except that the system is not working properly. In spite of this general shortcoming, in a few specific cases inferences may occasionally be drawn regarding the location of dysfunction within the system. Examples of these instances will be presented below.

In contrast to evoked potential techniques, single cell analysis (microelectrode studies) provides the opportunity to test directly the functional integrity of particular cell types in particular brain areas. These techniques provide information which is complementary to evoked potential techniques. Excellent examples of the unique and important contributions made by single cell analyses have been presented by Lowndes in this symposium. While essential for characterizing the detailed nature of toxicant-induced dysfunction, microelectrode studies present many practical problems. From a toxicology screening perspective, the major problem is one of sampling (Towe and Harding, 1970). Microelectrodes tend to sample activity from cells which are producing action potentials at the time that the investigator is placing the electrode. The manner in which studies are normally performed is that an electrode is lowered into the desired structure until action potentials are observed. Whether the activity of a particular cell is recorded depends in a direct way upon the size of the cell. Whether the activity of a particular *type* of cell is recorded depends also upon how many of them there are. Hunting for cells with a microelectrode is therefore somewhat like shooting fish in a barrel, where, relative numbers being equal, there is a tendency to hit only the big ones. Consequently, any toxicant which selectively affected small cells could produce major functional changes which could be missed, since the affected cells would be selectively missed by the recording electrode. Similarly, if the toxicant affected large cells, but the effect was to render a certain percentage of them nonfunctional (no spontaneous activity, no response to stimulation), these would never be recorded. Only the normal ones would be recorded (since they would be producing action potentials), and the conclusion would be drawn that cells in this area were not affected by the treatment. From a practical standpoint it would be very difficult to argue that failure of a particular electrode penetration to record any cells at all was a result of the exposure, and not merely a result of (a) bad luck (i.e., no fish in that part of the barrel), or (b) a bad electrode (a not uncommon occurrence). A further problem is choosing the brain area from which to record. While evoked potential studies may allow virtually simultaneous sampling of many areas, sampling of even a single area of brain with microelectrode techniques requires an extraordinary dedication of time and resources. Finally, there is the problem of the unit of analysis. In most toxicology experiments the appropriate unit of analysis is either the whole animal or group of whole animals (litters). In most microelectrode studies the unit of analysis is the single cell, and an experiment reporting data from 100 cells rarely includes sufficient detail to allow assessment of the number of successful recordings obtained from the "typical" animal. If the level of analysis was changed from the cell to the whole animal, many cells would have to be sampled in order to characterize the population of cells from a given animal, and this would be a laborious process indeed.

Implied in the preceding paragraph is that microelectrode studies are technically difficult. Completion of a successful study in normal animals requires a high level of expertise as well as long periods of time. Adding the dimension of exposure to a potential neurotoxicant makes microelectrode studies enormously complex. The techniques are simply not practical for early stages of identification and characterization of neurotoxicity. However, when a system is known to be affected by a toxicant, and more detailed information about the nature of dysfunction is desirable, then microelectrode studies are essential.

COMMONLY USED SENSORY EVOKED POTENTIAL TECHNIQUES

The procedures described below are the most extensively used macroelectrode sensory evoked potential techniques. The techniques which will not be described (e.g., visual evoked potentials recorded from subcortical structures or auditory evoked responses deriving from cortical activity) are generally refinements or variants of the included ones and the reader should be able to evaluate them using principles derived from this discussion.

Brainstem Auditory Evoked Responses (BAERs)

The BAER is a relatively recent addition to the armamentarium of clinical neurologists. It is one of a group of evoked potentials which have been called "far-field" responses, because the electrodes record field potentials which are quite distant from their source. Indeed, because of this distance the potentials are so small that many trials must be averaged to detect the response amid the ongoing activity of brain tissue which is closer to the recording electrodes.

The BAER may be recorded from almost any location, although the precise shape and size of the waveform depends upon the stimulus properties and the recording location. In freely moving rats it is somewhat difficult to ensure that an auditory stimulus will be the same at the ear from trial to trial unless earphones are employed, and this may be technically difficult in some animal studies. Small head movements can significantly alter the properties of a stimulus applied in a "free field" manner (Marsh *et al.*, 1962), and the middle ear muscles can alter a stimulus once it reaches the ear (Hugelin *et al.*, 1960). The impact of these variables has not yet been adequately determined in the case of the BAER. A typical waveform recorded from humans is illustrated in Fig. 1. There is some disagreement regarding the neuronal generators of the different peaks in the waveform. However, it is commonly assumed that the first peak reflects activity in the auditory nerve, and that subsequent peaks reflect activity in brainstem and midbrain structures involved in the processing of auditory information (Jewett, 1970). Therefore, alterations in latency and amplitude of the first peak reflect changes in the peripheral auditory

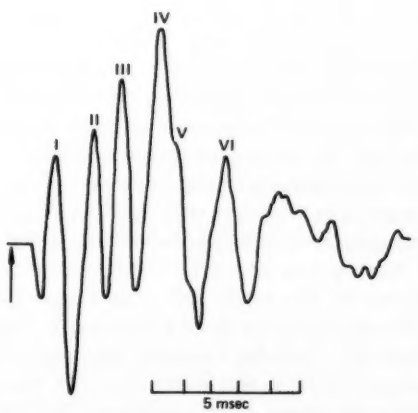

FIG. 1. A typical BAER waveform recorded from a human. While most evoked potential waveforms are represented as negative up, the BAER is usually, as here, represented positive up. The arrow indicates stimulus onset. Roman numerals designate commonly measured peaks. Normal variants of this waveform are described by Chiappa *et al.* (1979).

apparatus. Changes in latency which exceed those found in the first peak are generally taken to reflect central dysfunction (Kjaer, 1980).

In the neurological clinic, the BAER has been used for detecting specific loss in the auditory system (Parravicini *et al.,* 1982), localizing brain damage (Hari *et al.,* 1982; Kjaer, 1980; Karnaze *et al.,* 1982; Klug, 1982), aiding in diagnosis of multiple sclerosis (Barajas, 1982; Prasher *et al.,* 1982), and assessing brain death (Goldie *et al.,* 1981). In addition, it has been used during neurosurgery to provide the surgeon with an ongoing assessment of the integrity of the system (Greenberg and Ducker, 1982; Raudzens and Shetter, 1982).

While use of the BAER in toxicology is truly in its embryonic stage, its success in clinical settings, as well as its successful implementation in several toxicology laboratories, indicates that it will become an important tool (Rebert, 1980; Rebert and Sorenson, 1983). BAERs have been used to describe the effects of known ototoxic substances (Parravicini *et al.,* 1982). Rebert (1980) and Rebert *et al.* (1982) were among the first to use the BAER in toxicology, showing that the radiosensitizer drug misonidazole and hexane both cause a central conduction delay in the rat's auditory pathways. More recently, Rebert *et al.* (1983) demonstrated that chronic exposure to toluene produces a change in BAER intensity functions indicative of high-frequency hearing loss (Fig. 2). Those results were consistent with clear behavioral evidence of hearing loss above 8 kHz (Pryor *et al.,* 1983a). In this study rats were exposed to 1200 ppm toluene for 14 hr/day, 7 days/week, for 5 weeks. Damage appeared permanent, since it was detected many weeks after termination of the exposure. This conclusion was verified histologically in subsequent studies (Pryor *et al.,* 1983b).

Preliminary findings from the neurophysiology laboratories at EPA demonstrate alterations in BAERs of rats exposed to trimethyltin (TMT) (Fig. 3). All peak latencies were

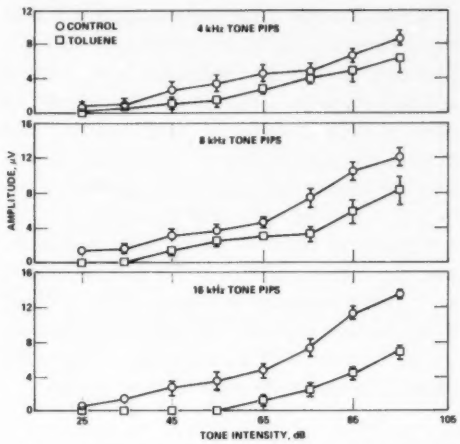

FIG. 2. Effects in rats of 5 weeks exposure to toluene on amplitude of the BAER. While evoked potential amplitudes are customarily measured as peak-to-peak differences for successive peaks, the amplitude of the entire waveform is here estimated using an RMS procedure. Values plotted are means ± SE for rats first exposed to toluene as weanlings. Testing occurred at eight different intensities and three different frequencies. Data replotted from Pryor *et al.* (1982).

increased and amplitudes were decreased, suggesting a peripheral locus of damage. These changes appear very rapidly after an acute administration of 6 mg/kg TMT (<24 hr), and the effects are evidently permanent. The electrophysiological effects are supported by behavioral studies showing impaired auditory startle responses following TMT administration (Howell *et al.,* 1981; Reiter *et al.,* 1983). Impaired BAERs have also been recorded from rats treated with triethyltin (TET) (Amochaev *et al.,* 1979). As with TMT, TET increased latencies of all peaks. An additional increase in the latencies of later peaks (peak IV minus peak I) suggested both central and peripheral contribution to dysfunction. Unlike TMT, the effects of TET disappeared within 2 weeks of removal from treatment.

Finally, Janssen *et al.* (1983) have demonstrated alterations in auditory function, as measured by BAERs, in rats exposed to the formamidine pesticide Chlordimeform

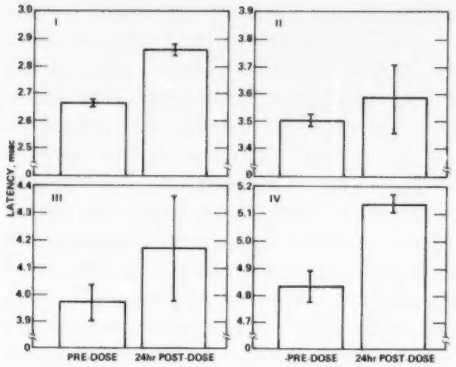

FIG. 3. Effects in rats of a single exposure to 6 mg/kg trimethyltin on BAER latencies. The data are based upon three animals with recordings obtained immediately before and 24 hr after exposure. Vertical bars: ±SE.

(CDMF). CDMF increased latencies of peaks II, III, and IV, but not peak I, suggesting that changes were of central origin and did not reflect inner ear damage (Fig. 4). These studies demonstrate the potential value of BAERs in toxicology, and suggest that the technique should be explored in more detail.

Somatosensory Evoked Potentials (SEPs)

In many respects the SEP is the most complex of the evoked potential techniques in common use. The response recorded from the human scalp, or cortex, contains both far-field and local components (Allison *et al.*, 1982). It may be obtained following stimulation of any sensory nerve in the peripheral nervous system, but obviously its time course and topography vary as a function of the locus of stimulation (Alpsan, 1981; Grisolia and Wiederholt, 1980). It is sensitive to size of the subject, since the distance between standard stimulus locations (e.g., the ankle) and the recording location (the scalp) varies considerably with size of the subject. While subject size is important for all evoked potential studies, there is much less variability in the distances between the inner ear and the brainstem in the case of the BAER, or the retina and the cortex in the case of the visual system, than there is between receptors and cortex in the somatosensory system. In spite of these considerations, the SEP has been a well-studied response in humans (Eisen, 1982; Josiassen *et al.*, 1982).

In the somatosensory system it is usually necessary to determine the appropriate stimulus intensity separately for each subject, since the desired intensity is usually a function of the extent to which the underlying peripheral nerve has been activated. For example, a stimulus which bears a constant relationship to the threshold intensity for producing the maximal compound action potential from the nerve should elicit consistent activation of the system across subjects, but individual differences in skin resistance, and distance of the nerve from the surface of the skin, make this value quite variable.

Figure 5 shows schematic SEPs derived from four human studies following stimulation of the median nerve, and from two rat studies following stimulation of the tail nerve.

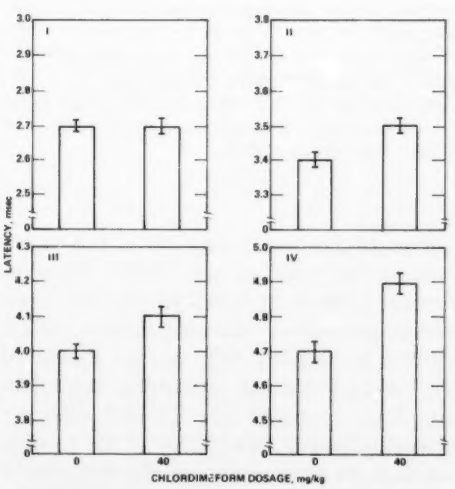

FIG. 4. Effects of Chlordimeform (CDMF) on BAER latencies. The data (from Janssen *et al.*, 1983) suggest a predominately central nervous system effect, because peak I was not affected.

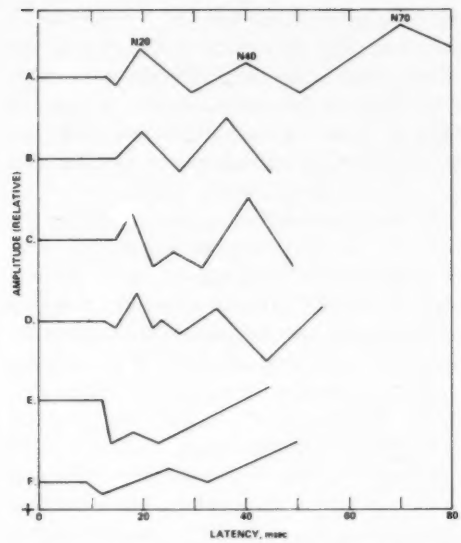

FIG. 5. Schematic somatosensory evoked potentials (SEPs) obtained from published latency data. Negativity is up. (A–D) Human SEPs recorded from scalp following stimulation of the contralateral median nerve. (A) Data from Obeso *et al.* (1980) based upon 40 normal subjects. (B) Giblin's (1980) "V" configuration, representative of about 72% of normal subjects. (C) Giblin's (1980) "W" configuration, representative of 28% of normal subjects. (D) Data from Hume and Cant (1978) based upon 21 normal subjects. The negative peak at about 25 msec was absent in 29% of cases. (E) Schematic of SEP recorded from rat skull following stimulation of the tail nerve, with rat anesthetized and tail warmed to 37°C (data from Howell *et al.*, 1982). (F) Same as (E) except rat unanesthetized and tail not warmed (data from Rebert and Sorenson, 1983).

Interpretation of the response is less direct than in the case of the BAER. Even in normal subjects, at least two "typical" configurations may be recorded (Giblin, 1980). Studies in humans with various lesions of the cortex, thalamus, brainstem, and spinal cord have suggested that the N20 wave recorded following stimulation of the median nerve at the wrist represents the first sign of cortical activity (Hume and Cant, 1978). The later peaks seem to reflect further cortical processing of the information. Alterations in peak latencies and amplitudes may reflect anything from changes in conduction velocity or fiber populations of the peripheral nerve involved to increased synaptic delay or loss of selected neurons in the spinal cord, brainstem, or thalamus. While the pattern of changes in amplitudes and latencies may not be diagnostic, it can be helpful. For example, Obeso *et al.* (1980) have reported that cortical lesions restricted to the primary sensorimotor area tend to produce increases in latency and decreases in amplitude of peaks N20, N40, and N70, while cortical lesions outside this area tended to produce increased amplitude and increased duration of these peaks. It should be clear that the SEP can provide a good measure of function/dysfunction anywhere in the chain of somatic sensation. If alterations are observed in the N20 response recorded at the scalp following stimulation of the median nerve at the wrist, then subsequent studies may be designed to ferret out the locus of dysfunction by evaluating the far field SEP (Allison *et al.*, 1982; Crespi *et al.*, 1982), recording from the peripheral nerves and spinal cord (Arezzo *et al.*, 1982), or stimulating at different sites.

In the neurological clinic SEPs have been used to characterize multiple sclerosis (Bottcher and Trojaborg, 1982; Alpsan, 1981) and focal lesions (Crespi *et al.*, 1982; Wong *et al.*, 1982) as well as to assess brain death (de la Torre, 1981). SEPs are also becoming routine monitoring procedures during neurosurgery (Lesser *et al.*, 1981; Macon *et al.*, 1982).

Since many neurotoxic substances produce dysfunction in the peripheral nervous system, it is not surprising that SEPs recorded from various locations along the somatosensory pathway have detected toxicity. Boyes and Cooper (1981) have shown that exposure to acrylamide produces alterations in the far-field SEP recorded from rats. Using the far-field SEP technique allowed the authors to detect alterations in the somatosensory system which were in addition to the known effects of acrylamide on the peripheral nerves. More recently Arezzo *et al.* (1982) have confirmed

these findings in monkeys, showing that somatosensory responses recorded from the cervical spinal cord detected acrylamide toxicity earlier than do responses recorded from the peripheral nerve.

Rebert *et al.* have included the SEP as part of an electrophysiological battery for assessment of neurotoxicity. In this context they investigated the effects of carbon disulfide, hexane, vincristine, maytansine, and *cis*-platinum upon the SEP recorded from the skull following electrical stimulation of the ventral caudal tail nerve in the rat. Significant SEP alterations were found in all cases, but only in the case of *cis*-platinum did the SEP technique appear to detect toxicity at lower dosages than other techniques included in the battery (Rebert and Sorenson, 1983; Rebert *et al.*, in preparation).

Howell *et al.* (1982) have demonstrated that SEPs detect dysfunction induced by TMT. Figure 6 illustrates these findings, which were characterized by increased latencies. The results were particularly significant since they contributed to the growing evidence that this compound, formerly thought to be largely a limbic system neurotoxicant (Brown *et al.*, 1979), also affects sensory systems. Indeed, most of the early evidence that TMT produced sensory dysfunction is derived from evoked potential investigations (Dyer, 1982). Morphological confirmation of these sensory defects has been provided more recently by Chang and Dyer (1983).

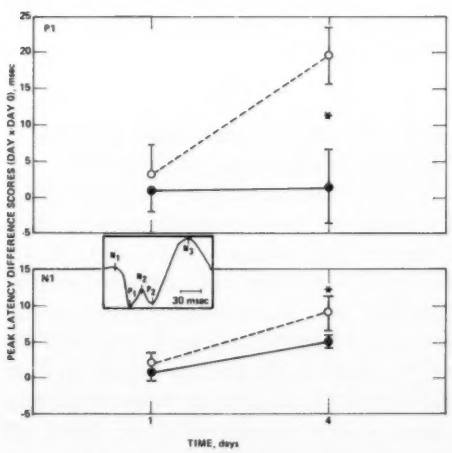

FIG. 6. Effects in rats of a single exposure to 7 mg/kg TMT on the SEP. The data indicate a progressive increase in latency of peaks P1 and N1 with time since dosing. Redrawn from Howell *et al.* (1982).

From the above discussion it is clear that the SEP has already shown promise in detecting and characterizing neurotoxicity. Further development of the method for toxicology will require that some attention is given to producing a standardized recording paradigm useful for rats, and that some agreement is reached regarding the morphology of a "prototype" SEP waveform.

Flash Evoked Potentials (FEPs)

Evoked potential approaches to problems of neurotoxicology have usually included assessment of the visual system. The visual system is unique in that it is embryologically a purely CNS system, while other sensory systems contain peripheral nervous system components. There are two main types of paradigms which have been used, the flash evoked potential (FEP) and the pattern reversal evoked potential (PREP). These will be considered separately here.

FEPs have been used by several laboratories for routine evaluation of neurotoxicity. Selection of this particular measure is usually based upon the relative ease of controlling the stimulus properties at the receptor compared to other systems. Pupil dilation with topical atropine allows a bright flash to maximally activate the retina, and surrounding the subject with mirrors minimizes the effect of head movements. The major problem in ensuring reproducibility of the stimulus from trial to trial and subject to subject is one of dark adaptation. If testing occurs in an environment which is darker than the ambient environment, then dark adaptation must be allowed to occur before testing can begin. Unfortunately, many investigators ignore this control.

Because it has been used so extensively, the FEP has been characterized both with respect to a variety of pharmacological manipulations (e.g., Dyer *et al.*, 1981) and with regard to values reflecting gender, strain, and stimulus intensity norms (Dyer and Swartzwelder, 1978). Because of the data base, some comparisons of amplitude and latency values across experiments are possible. Figure 7 illustrates a typical FEP. Generally, the rat is surgically prepared for study at least a week in advance. At the time of study it is placed in a recording chamber with mirrors on three walls and a strobe light mounted on the fourth (Dyer and Annau, 1977). If there is any likelihood that the compound under study would alter pupil diameter, the pupils should be dilated with atropine.

In human studies the FEP has been used much less frequently than the PREP. PREPs are claimed to detect neurological dysfunction more effectively than FEPs (e.g., Sokol, 1980), although few real comparisons have been made. The value of these two tools in the neurological clinic will be discussed in the next section.

Cataloging the influence of various toxicants upon the FEP is beyond the scope of this paper. What follows is a (largely personal) sample from the available literature. All of the examples are drawn from studies of adult hooded rats, and they have been selected to represent effects which may result from a variety of different compounds and dosing regimen (including perinatal exposure).

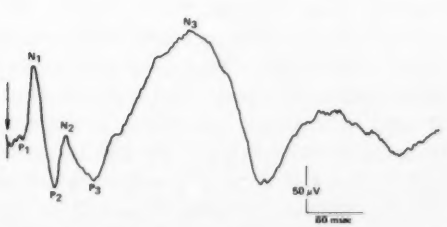

FIG. 7. Typical flash evoked potential (FEP) recorded from the skull of a hooded rat. Arrow indicates flash. Negative deflections are upward. Peaks are identified according to common nomenclature (e.g., Dyer, 1980).

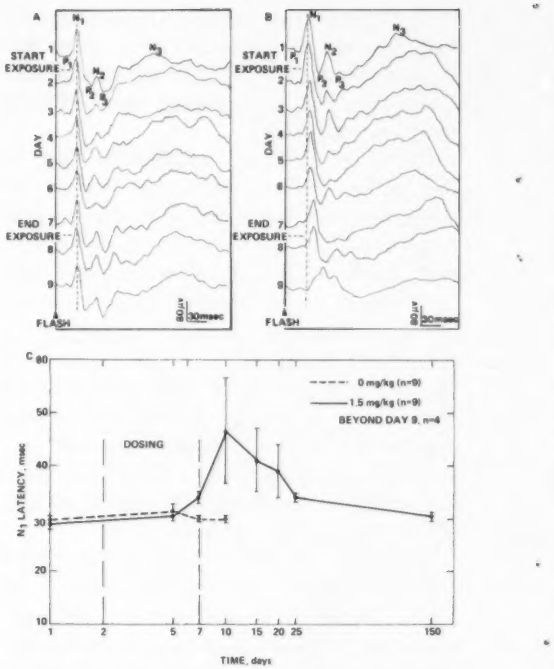

FIG. 8. Effects in rats of six daily ip injections of 1.5 mg/kg TET on the FEP. (A) FEPs recorded from a single control animal on each of 9 successive test days; (B) FEPs recorded from a single treated rat on 9 successive test days; (C) group means (±SE) of the first negative peak (N1) plotted for both treated and control groups over the course of the experiment. Data from Dyer and Howell (1982).

Adult exposure paradigms. Triethyltin (TET), a compound known to produce vacuolation of myelin and edema, was injected (ip, 1.5 mg/kg/day) into rats daily for 6 consecutive days. FEPs were recorded daily before, during, and after treatment. Figure 8 illustrates the results. Figure 8a shows daily recordings from one control rat, and Fig. 8b shows progressive changes in the waveforms of one dosed rat. Figure 8c illustrates the group mean peak latency for the first negative peak (N1) of the response. The figures show that several days

of treatment were required to initiate any effect, but that once elicited the effect outlasted the treatment by some time. An increase in the latency of the first peak in the response is consistent with the interpretation that myelin has been compromised, although other interpretations are possible (Dyer and Howell, 1982).

Unlike TET, trimethyltin (TMT) produces loss of neuron cell bodies. While morphological studies had previously concluded that TMT-induced damage is restricted largely to the limbic system (Brown *et al.*, 1979), the use of a FEP test in a screening context detected what turned out to be retinal damage. In this study, rats were treated with TMT, and recordings were made immediately before and 1, 4, 8, and 16 days following dosing. Statistical analysis revealed that effects were not time dependent within this range of test time, and Fig. 9 therefore shows the alterations in peak latency collapsed across the different post-treatment times. Alterations appeared in the earliest peak of the response, suggesting the possibility of subcortical changes. To test the hypothesis that the alterations were retinal in origin, a second study was done with electrodes placed in the optic nerve as well as over the visual cortex. As would be expected if there was retinal damage, the magnitude and direction of change observed in the cortex were also present in the optic tract recordings (Dyer *et al.*, 1982). Subsequent neuropathological examination by Chang demonstrated retinal lesions in these animals, thereby confirming the physiologically predicted results (Chang and Dyer, 1983). Due to the loss of retinal cells, the evoked potential changes can be expected to be permanent.

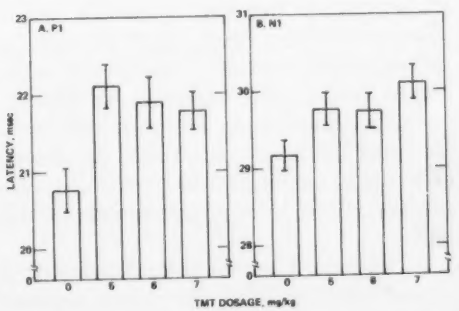

FIG. 9. Effects in rats of a single injection of TMT on the FEP. The data indicate increases in P1 and N1 latencies, thereby suggesting altered inputs to the cortex. Data from Dyer *et al.* (1982).

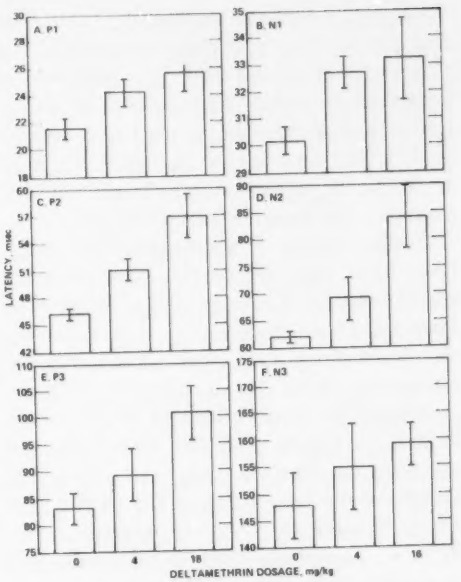

FIG. 10. Effects in rats of a single injection of deltamethrin upon FEP latencies. As with TMT, the data suggest altered inputs to the cortex. Data from Dyer and Boyes (unpublished).

Deltamethrin is a synthetic pyrethrin which is known to disrupt sodium conductance (Narahashi, 1971), but is not known to have any particular effects upon the visual system. A recent study (Dyer and Boyes, unpublished) has demonstrated increased latencies of FEPs recorded 30 min following a single administration of deltamethrin. These findings are summarized in Fig. 10. The time course and origin of these changes has not yet been determined.

Perinatal exposure paradigms. In some respects, the most impressive demonstrations of the power of the FEP for detection of neurotoxicity come from studies in which exposure occurred many weeks before testing. Such is the case in the perinatal exposure studies to be reviewed here. Three different exposure paradigms will be discussed.

A wide variety of neurobehavioral alterations have been reported in rats following administration of a single dosage of TET on Postnatal Day 5 (Reiter *et al.*, 1981). Among the effects which have appeared at the lowest dosage are those demonstrated in FEP recordings (Dyer *et al.*, 1981). In great contrast to an acute exposure to TET, early postnatal exposure produces a long-term change in latency of the later peaks of the FEP. These effects, illustrated in Fig. 11, suggest a very different mechanism than for the acute adult exposure effects described earlier. Here the damage seems to be cortical, since changes are largest in the latest peaks.

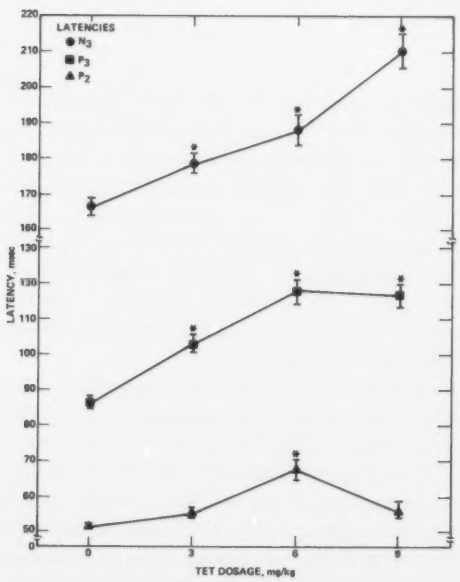

FIG. 11. Effects in adult rats of a single early postnatal injection of TET on FEP latencies. The magnitude of changes was greatest in late peaks. Early peaks were virtually unaffected. Replotted from Dyer *et al.* (1981).

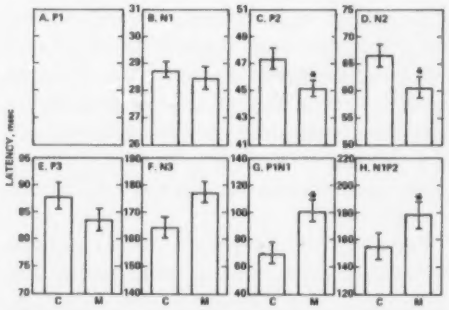

FIG. 12. Effects in adult rats of a single Gestational Day 7 administration of methyl mercury (mg/kg) on FEP amplitudes and latencies. P1 latencies were not recorded in this study. P2 and N2 latencies were decreased by the treatment. Data were replotted from Dyer *et al.* (1978).

In addition to a single early postnatal exposure to a toxic compound, a single prenatal exposure has also been demonstrated to produce permanent alterations in the FEP. In one study (Dyer *et al.*, 1978) rats were administered a single dosage of methyl mercury on Gestational Day 7, and FEP recordings were made when they reached adulthood. The results, summarized in Fig. 12, demonstrate a significant increase in the amplitude of the primary peak of the response, and a significant decrease in the latency of peaks P2 and N2. In this case, a selective loss of slowly conducting fibers could account for the decreased latencies. A number of mechanisms might cause increased amplitudes, including hypothermia, decreased inhibition, increased synchrony, etc. While the finding of increased amplitude is not novel, one may not yet attach to it a mechanism in this study.

A number of studies have demonstrated altered FEPs in adult rats given repeated perinatal exposures to lead (Fox *et al.*, 1977; Feeney *et al.*, 1979; Winneke, 1979). In one such study (Burdette, 1983), rats exposed at various times during either the prenatal or

early postnatal period displayed decreased N1 and P2 latencies. While interpretation of these data in terms of the underlying causes may be difficult, they provide convincing evidence that the visual system is altered in a permanent way by perinatal exposure to lead.

Pattern Reversal Evoked Potentials (PREPs)

FEPs are produced by turning on and off an intense stimulus. It is also possible to produce visual evoked potentials by changing a pattern of bright and dark areas on a screen without altering the overall level of illumination in the visual field. While there are several methods of stimulus presentation in use, the most commonly used method is reversing (black for white and white for black) the checks on a checkerboard display, or the bars in a horizontal or vertical array. Potentials generated by this procedure are referred to as pattern reversal evoked potentials, or PREPs. A representative group average PREP, which has a simpler waveform than a FEP, is illustrated in Fig. 13.

In the neurological clinic, alterations in PREPs have been demonstrated in cases of multiple sclerosis (Neetens *et al.*, 1979), Huntington's disease (Ellenberger *et al.*, 1978), Parkinson's disease (Bodis-Wollner and Yahr, 1978; Mintz *et al.*, 1981), and a number of focal lesions of the visual system (Arseni *et al.*, 1979; Hess *et al.*, 1982; Kooi *et al.*, 1973; Maitland *et al.*, 1982; Nikoskelainen and Falck, 1982; Streletz *et al.*, 1981). FEPs have been effective in many of the same cases (Neetens *et al.*, 1979; Wilson and Keyser, 1980), but the frequency of correct diagnoses may be somewhat greater with PREPs than FEPs. In addition, by systematically varying the size of the pattern and observing the correlated changes in amplitude of PREPs, estimates can be made of visual acuity (Boyes *et al.*, 1982). Therefore analysis of PREPs may provide not only greater sensitivity, but also data which reflect different aspects of visual function than those provided by FEPs.

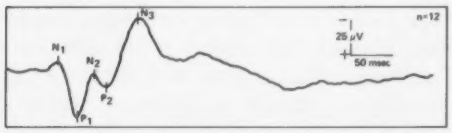

FIG. 13. Typical pattern reversal evoked potential (PREP) recorded from a hooded rat. Note the smaller amplitude, longer latency, and smoother initial peaks compared to the FEP in Fig. 7. Negativity is upward, and peaks are labeled according to the nomenclature of Boyes *et al.* (1982).

In spite of these potential advantages of PREPs, they have not often been used for assessment of neurotoxicity. While it is relatively easy to ensure that a human subject fixates and focuses upon a pattern, it is much more difficult to ensure that an animal does, at least not without some training and/or restraining. Consequently, controlling the stimulus at the receptor (i.e., making sure that across trials within subjects, and between subjects, roughly the same stimulus is presented on each trial) is a problem. Recently there have been several successful efforts to record PREPs in rats (Boyes and Dyer, 1983; Onofrj *et al.*, 1982). Preliminary studies using PREPs as a neurotoxicological method suggest that the added difficulty may be worth the effort.

A comparison between the effects of TET on PREPs and the effects of TET on FEPs illustrates that in this case PREPs are more useful. Each technique was used in the manner which is presently considered to be most effective (e.g., rats were restrained in a harness for PREP recording, but unrestrained in a mirror box for FEP recording). The findings (Boyes and Dyer, 1983) indicated that PREPs detected a type of effect not detected by the FEP (decreased amplitudes), and that the type of effect shown previously to be detected by the FEP (increased latencies) is detected

with a lower probability value when the PREP is used.

It will be recalled that the formamidine pesticide CDMF produces alterations in the BAER. Dyer and Boyes have recently shown (1983) that CDMF also produced significant alterations in peak latencies of the FEP and the PREP. However, CDMF produced extraordinary increases in the amplitude of PREP peaks, but did not alter FEP amplitudes. The effects of CDMF on PREPs and FEPs are compared in Fig. 14. Preliminary data suggest that these effects of CDMF on PREPs do not result from some major known effects of CDMF: monoamine oxidase inhibition and local anesthetic action. While the significance of the evoked potential alterations remains to be determined, it is clear that CDMF exerts a potent influence on the functional integrity of the visual system.

In addition to these findings, Fox *et al.* (1983) have recently reported that perinatal exposure to lead alters PREPs, and that the nature of the alterations is consistent with a decrease in the visual acuity of the rats.

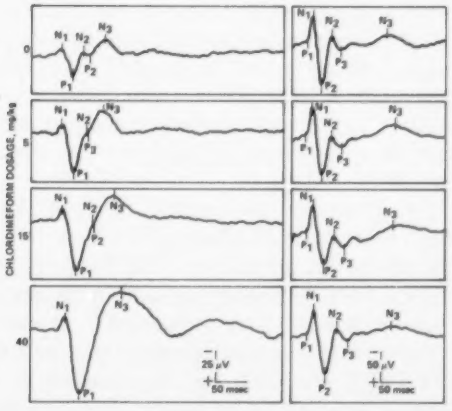

FIG. 14. Effects in adult rats of a single acute exposure to Chlordimeform (CDMF) on (A) PREPs and (B) FEPs. CDMF produced increases in latency of both PREPs and FEPs, but only affected amplitude of PREPs. Waveforms shown are averages of the entire groups at the indicated dosages.

While the above data indicate that the PREP is an important test, it is also important to note that it does not always detect alterations better or even as well as the FEP. Preliminary data from our lab have failed to detect any alterations in PREPs following exposure to deltamethrin in the same animals from which the significant FEP alterations noted above were observed.

CONCLUSIONS AND PROSPECTS

From the above discussion, it is clear that sensory-evoked potentials have value for the detection and characterization of neurotoxicity. They provide a relatively rapid assessment of the functional integrity of sensory systems, and in some cases results from animal studies may be extrapolated in a very direct way to human studies. Similarly, our knowledge of alterations in sensory-evoked potentials reported in clinical neurology assists in interpretation of animal data, providing human disease correlates of toxicant-induced alterations.

Despite their obvious immediate value, considerable work remains before sensory-evoked potentials achieve their full value for toxicology. Detailed discussion of the future requirements for research on sensory-evoked potentials is beyond the scope of this paper. However, several key areas may be profitably identified.

At present, there are only a few criteria available which direct the investigator to the appropriate sensory-evoked potential technique. Of course, if prior knowledge suggests that a particular system is affected by a particular toxicant, then no difficulty exists. However, it would be extremely useful to have a data base which was sufficiently extensive to allow some judgment that, for example, if any sensory system is to be affected the visual system would be. Thus, to screen for damage to all sensory systems, one could first test the visual system. If it produced

negative results, then reasonable assurances could be given that sensory systems were not generally affected. Several papers have presented sensitivity comparisons between different evoked potential methods (e.g., Goldie *et al.*, 1981; Newlon *et al.*, 1982; Oepen *et al.*, 1981; Purves *et al.*, 1981). In a recent study (Nuwer *et al.*, 1983) PREPs, BAERs, and SEPs were recorded from 45 patients with classic cases of certain inherited disorders which share ataxia as a frequent and prominent sign. In all disorders, evoked potential alterations were found. PREPs were abnormal in most cases, while BAERs and SEPs were abnormal for only some of the 10 disorders examined.

In addition to sensitivity, the issue of practicality (cost effectiveness) must be addressed. For example, while the SEP may detect toxicity very well, if it is more difficult and more expensive to perform the studies well and if somatosensory dysfunction correlates well with visual dysfunction, then it may be more sensible to test only the visual system. Similarly, if two tests provide similar sensitivity, but interpretation of one is more straightforward than interpretation of the other, then the choice is easily made. Presently, sufficient data do not exist to make these assessments.

Another group of issues in desperate need of attention concerns the validation of the evoked potential techniques. Validation is a concept which can be understood at many levels. In general the term refers to the extent to which a test has been shown to measure what it is supposed to measure. In the context of evoked potentials one may ask: (1) are evoked potentials valid indicators of the functional integrity of the sensory system used to produce them; and (2) are evoked potentials valid indicators of neurotoxicity? The second case is of greatest concern here. More specifically, we need to know (1) whether toxicity to the system is invariably detected by the technique; (2) whether detailed consideration of the nature of amplitude and latency alterations can tell more than that the system is not working properly, i.e., to what extent can we pinpoint a functional problem by knowing that a particular amplitude or latency is increased or decreased; (3) how well data obtained from rat EPs can be generalized to human neurotoxicity, and, perhaps most important, (4) what the health consequences of disordered evoked potentials are.

Certainly answers to the above issues can come only with a considerable effort involving many laboratories investigating many compounds with many different techniques. The growing interest in the use of these techniques provides hope that such an effort may in fact be realized.

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REFERENCES

ALLISON, T., WOOD, C. C., MCCARTHY, G., HUME, A. L., AND GOFF, W. R. (1982). Short-latency somatosensory evoked potentials in man, monkey, cat and rat: Comparative latency analysis. In *Clinical Applications of Evoked Potentials in Neurology* (J. Courjon, F. Mauguiere, and M. Revol, eds.). Raven Press, New York.

ALPSAN, D. (1981). The effect of the selective activation of different peripheral nerve fiber groups on the somatosensory evoked potentials in the cat. *Electroencephalogr. Clin. Neurophysiol.* **51,** 589–598.

AMOCHAEV, A., JOHNSON, R. C., SALAMY, A., AND SHAH, S. N. (1979). Brain stem auditory evoked potentials and myelin changes in triethyltin-induced edema in young adult rats. *Exp. Neurol.* **66,** 629–635.

AREZZO, J. C., SCHAUMBURG, H. H., VAUGHAN, H. G., JR., SPENCER, P. S., AND BARNA, J. (1982). Hind limb somatosensory evoked potentials in monkey: The effects of distal axonopathy. *Ann. Neurol.* **12,** 24–32.

ARSENI, C., CRIGHEL, E., MATEI, M., AND DINU, M. (1979). Influence of temporal lobe lesions on photic-evoked responses in occipital visual areas. *Appl. Neurophysiol.* **42,** 145–152.

BARAJAS, J. J. (1982). Evaluation of ispilateral and

contralateral brainstem auditory evoked potentials in multiple sclerosis patients. *J. Neurol. Sci.* **54,** 69–78.

BECK, E. C., DUSTMAN, R. E., AND LEWIS, E. G. (1975). The use of the averaged evoked potential in the evaluation of central nervous system disorders. *Int. J. Neurol.* **9,** 211–232.

BODIS-WOLLNER, I., AND YAHR, M. D. (1978). Measurements of visual evoked potentials in Parkinson's disease. *Brain* **101,** 661–671.

BOTTCHER, J., AND TROJABORG, W. (1982). Follow-up of patients with suspected multiple sclerosis: A clinical and electrophysiological study. *J. Neurol. Neurosurg. Psychiatr.* **45,** 809–814.

BOYES, W. K., AND COOPER, G. P. (1981). Acrylamide neurotoxicity: Effects on far-field somatosensory evoked potentials in rats. *Neurobehav. Toxicol. Teratol.* **3,** 487–490.

BOYES, W. K., DYER, R. S., AND HOWELL, W. E. (1982). Visual acuity in rats: Rapid assessment using pattern reversal evoked potentials. *Neurosci. Abstr.* **8,** 350.

BOYES, W. K., AND DYER, R. S. (1983). Pattern reversal evoked potentials detect triethyltin toxicity better than flash evoked potentials. *Toxicologist* **3,** 168.

BROWN, A. W., ALDRIDGE, W. N., STREET, B. W,. AND VERSCHOYLE, R. D. (1979). The behavioral and neuropathological sequelae of intoxication by trimethyltin compounds. *Amer. J. Pathol.* **97,** 59–82.

BURDETTE, L. J. (1983). *The Effects of Asymptomatic Lead Exposure during Different Developmental Stages in Rats: Behavior and Electrophysiology.* Unpublished doctoral dissertation.

CHANG, L. W., AND DYER, R. S. (1983). Trimethyltin induced pathology in sensory neurones. *Neurobehav. Toxicol. Teratol.* **5,** 673–696

CHIAPPA, K. H., GLADSTONE, K. J., AND YOUNG, R. R. (1979). Brainstem auditory evoked responses. Studies of waveform variations in 50 normal human subjects. *Arch. Neurol.* **36,** 81–87.

CRESPI, V., MANDELLI, A., AND MINOLI, G. (1982). Short-latency somatosensory-evoked potentials in patients with acute focal vascular lesions of the supratentorial somesthetic pathways. *Acta Neurol. Scand.* **65,** 274–279.

DE LA TORRE, J. C. (1981). Evaluation of brain death using somatosensory evoked potentials. *Biol. Psychiatr.* **16,** 931–935.

DYER, R. S. (1980). Effects of prenatal and postnatal exposure to carbon monoxide on visually evoked responses in rats. In *Neurotoxicology of the Visual System* (W. H. Merigan and B. Weiss, eds.), pp. 17–33. Raven Press, New York.

DYER, R. S. (1982). Physiological methods for assessment of trimethyltin exposure. *Neurobehav. Toxicol. Teratol.* **4,** 659–664.

DYER, R. S., AND ANNAU, Z. (1977). Flash evoked potentials from rat superior colliculus. *Pharmacol. Biochem. Behav.* **6,** 453–459.

DYER, R. S., AND BOYES, W. K. (1983). Chlordimeform differentially affects pattern reversal-evoked and flash evoked potentials in rats. *Toxicologist* **3,** 13.

DYER, R. S., ECCLES, C. U., AND ANNAU, Z. (1978). Evoked potential alterations following prenatal methyl mercury exposure. *Pharmacol. Biochem. Behav.* **8,** 137–141.

DYER, R. S., AND HOWELL, W. E. (1982). Acute triethyltin exposure: Effects on the visual evoked potential and hippocampal afterdischarge. *Neurobehav. Toxicol. Teratol.* **4,** 259–266.

DYER, R. S., HOWELL, W. E., AND MACPHAIL, R. C. (1981). Dopamine depletion slows retinal transmission. *Exp. Neurol.* **71,** 326–340.

DYER, R. S., HOWELL, W. E., AND REITER, L. W. (1981). Neonatal triethyltin exposure alters adult electrophysiology. *Neurotoxicology* **2,** 603–611.

DYER, R. S., HOWELL, W. E., AND WONDERLIN, W. F. (1982). Visual system dysfunction following acute trimethyltin exposure in rats. *Neurobehav. Toxicol. Teratol.* **4,** 191–195.

DYER, R. S., AND SWARTZWELDER, H. S. (1978). Sex and strain differences in the visual evoked potentials of albino and hooded rats. *Pharmacol. Biochem. Behav.* **9,** 301–306.

EISEN, A. (1982). The somatosensory evoked potential. *Canad. J. Neurol. Sci.* **9,** 65–77.

ELLENBERGER, C., PETRO, D. J., AND ZIEGLER, S. B. (1978). The visual evoked potential in Huntington's disease. *Neurology* **28,** 95–97.

FEENEY, D. M., LONGO, J. F., CORDEN, M. A., ZENICK, H., AND PADICK, R. (1979). Detection of the effects of lead exposure by visual evoked response latency. *Physiol. Psychol.* **7,** 143–145.

FOX, D., LEWKOWSKI, J., AND COOPER, G. (1977). Acute and chronic effects of neonatal lead exposure on development of the visual evoked response in rats. *Toxicol. Appl. Pharmacol.* **40,** 449–461.

FOX, D. A., COSTA, L., AND WRIGHT, A. A. (1983). Spatial vision deficits in adult rats following developmental lead exposure. *Toxicologist* **3,** 69.

GIBLIN, D. R. (1980). Scalp-recorded somatosensory evoked potentials. In *Electrodiagnosis in Clinical Neurology* (M. J. Aminoff, ed.), pp. 414–450. Churchill Livingstone, New York.

GOLDIE, W. D., CHIAPPA, K. H., YOUNG, R. R., AND BROOKS, E. B. (1981). Brainstem auditory and short-latency somatosensory evoked responses in brain death. *Neurology* **31,** 248–256.

GREEN, J. B., AND WALCOFF, M. R. (1982). Evoked potentials in multiple sclerosis. *Arch. Neurol.* **39,** 696–697.

GREENBERG, R. P., AND DUCKER, T. B. (1982). Evoked potentials in the clinical neurosciences. *J. Neurosurg.* **56,** 1–18.

GRISOLIA, J. S., AND WIEDERHOLT, W. C. (1980). Short latency somatosensory evoked potentials from radial,

median and ulnar nerve stimulation in man. *Electroencephalogr. Clin. Neurophysiol.* **50,** 375–381.

HARI, R., SULKAVA, R., AND HALTIA, M. (1982). Brainstem auditory evoked responses and alpha-pattern coma. *Ann. Neurol.* **11,** 187–189.

HESS, CH. W., MEIENBERG, O., AND LUDIN, H. P. (1982). Visual evoked potentials in acute occipital blindness, diagnostic and prognostic value. *J. Neurol.* **227,** 193–200.

HOWELL, W. E., DYER, R. S., WONDERLIN, W. F., KIDD, K., AND REITER, L. W. (1981). Sensory system effects of acute trimethyltin (TMT) exposure. *Toxicologist* **1,** 43.

HOWELL, W. E., WALSH, T. J., AND DYER, R. S. (1982). Somatosensory dysfunction following acute trimethyltin exposure. *Neurobehav. Toxicol. Teratol.* **4,** 197–201.

HUGELIN, A., DUMONT, S., AND PAILLAS, N. (1960). Formation reticulaires et transmission des informations auditives au niveau de l'orielle moyenne et des voies acoustiques centrales. *Electroencephalogr. Clin. Neurophysiol.* **12,** 797–818.

HUME, A. L., AND CANT, B. R. (1978). Conduction time in central somatosensory pathways in man. *Electroencephalogr. Clin. Neurophysiol.* **45,** 361–375.

JANSSEN, R., BOYES, W. K., AND DYER, R. S. (1983). The effects of chlordimeform on the brainstem auditory evoked response in rats. In *Developments in the Science and Practice of Toxicology* (A. W. Hayes, R. C. Schnell, and T. S. Miya, eds.), pp. 533–536. Elsevier, North Holland.

JEWETT, D. L. (1970). Volume-conducted potentials in response to auditory stimuli as detected by averaging in the cat. *Electroencephalogr. Clin. Neurophysiol.* **28,** 609–618.

JOSIASSEN, R. C., SHAGASS, C., MANCALL, E. L., AND ROEMER, R. A. (1982). Somatosensory evoked potentials in huntington's disease. *Electroenceph. Clin. Neurophysiol.* **54,** 483–493.

KARNAZE, D. S., MARSHALL, L. F., MCCARTHY, C. S., KLAUBER, M. R., AND BICKFORD, R. G. (1982). Localizing and prognostic value of auditory evoked responses in coma after closed head injury. *Neurology* **32,** 299–302.

KJAER, M. (1980). Localizing brain stem lesions with brain stem auditory evoked potentials. *Acta. Neurol. Scand.* **61,** 265–274.

KLUG, N. (1982). Brainstem auditory evoked potentials in syndromes of decerebration, the bulbar syndrome and in central death. *J. Neurol.* **227,** 219–228.

KOOI, K. A., YAMADA, T., AND MARSHALL, R. E. (1973). Field studies of monocularly evoked cerebral potentials in bitemporal hemianopsia. *Neurology* **23,** 1217–1225.

LESSER, R. P., LUEDERS, H., HAHN, J., AND KLEM, G. (1981). Early somatosensory potentials evoked by median nerve stimulation: Intraoperative monitoring. *Neurology* **31.** 1519–1523.

MACON, J. B., POLETTI, C. E., SWEET, W. H., OJEMANN, R. G., AND ZERVAS, N. T. (1982). Conducted somatosensory evoked potentials during spinal surgery. Part 2. Clinical applications. *J. Neurosurg.* **57,** 354–359.

MAITLAND, C. G., AMINOFF, M. J., KENNARD, C., AND HOYT, W. F. (1982). Evoked potentials in the evaluation of visual field defects due to chiasmal or retrochiasmal lesions. *Neurology* **32,** 986–991.

MARSH, J. T., WORDEN, F. G., AND HICKS, L. (1962). Some effects of room acoustics on evoked auditory potentials. *Science (Washington, D.C.)* **137,** 280–284.

MINTZ, M., TOMER, R., RADWAN, H., AND MYSLOBODSKY, M. S. (1981). Visual evoked potentials in hemiparkinsonism. *Electroencephalogr. Clin. Neurophysiol.* **52,** 611–616.

NARAHASHI, T. (1971). Mode of action of pyrethroids. *Bull. W.H.O.* **44,** 337–345.

NEETENS, A., HENDRATA, Y., AND VAN ROMPAEY, J. (1979). Pattern and flash visual evoked responses in multiple sclerosis. *J. Neurol.* **220,** 113–124.

NEWLON, P. G., GREENBERG, R. P., HYATT, N. S., ENAS, G. G., AND BECKER, D. P. (1982). The dynamics of neuronal dysfunction and recovery following severe head injury assessed with serial multimodality evoked potentials. *J. Neurosurg.* **57,** 168–177.

NIKOSKELAINEN, E., AND FALCK, B. (1981). Do visual evoked potentials give relevant information to the neuro-opthalmological examination in optic nerve lesions. *Acta Neurol. Scand.* **66,** 42–57.

NUWER, M. R., PERLMAN, S. L., PACKWOOD, J. W., AND KARK, R. A. P. (1983). Evoked potential abnormalities in the various inherited ataxias. *Ann. Neurol.* **13,** 20–27.

OBESO, J. A., MARTI-MASSO, J. F., AND CARRERA, N. (1980). Somatosensory evoked potentials: Abnormalities with focal brain lesions remote from the primary sensorimotor area. *Electroencephalogr. Clin. Neurophysiol.* **49,** 59–65.

OEPEN, G., DOERR, M., AND THODEN, U. (1981). Visual (VEP) and somatosensory (SSEP) evoked potentials in Huntington's chorea. *Electroencephalogr. Clin. Neurophysiol.* **51,** 666–670.

ONOFRJ, M., BODIS-WOLLNER, I., AND BOBAK, P. (1982). Pattern visual evoked potentials in the rat. *Physiol. Behav.* **28,** 227–230.

PARRAVICINI, L., ARPINI, A., BAMONTE, F., MARZANATTI, M., AND ONGINI, E. (1982). Comparative ototoxicity of amikacin, gentamicin, netilmicin and tobramycin in guinea pigs. *Toxicol. Appl. Pharmacol.* **65,** 222–230.

PRASHER, D. K., SAINZ, M., AND GIBSON, W. P. R. (1982). Binaural voltage summation of brainstem auditory evoked potentials: An adjunct to the diagnostic criteria for multiple sclerosis. *Ann. Neurol.* **11,** 86–91.

PRYOR, G. T., DICKINSON, J., HOWD, R. A., AND REBERT, C. S. (1983a). Transient cognitive deficits and high frequency hearing loss in weanling rats

exposed to toluene. *Neurobehav. Toxicol. Teratol.* **5,** 53–57.

PRYOR, G. T., HOWD, R. A., AND REBERT, C. S. (1982). *Developmental Long-Term Effects of Inhalants in Animals.* Annual Report 2, NIDA Contract 271-80-3712. SRI International, Menlo Park.

PRYOR, G. T., HOWD, R. A., AND REBERT, C. S. (1983b). *Developmental Long-Term Effects of Inhalants in Animals.* Quarterly Report 9, NIDA Contract 271-80-3712. SRI International, Menlo Park.

PURVES, S. J., LOW, M. D., GALLOWAY, J. AND REEVES, B. (1981). A comparison of visual, brainstem auditory, and somatosensory evoked potentials in multiple sclerosis. *Canad. J. Neurol. Sci.* **8,** 15–19.

RAUDZENS, P. A., AND SHETTER, A. G. (1982). Intraoperative monitoring of brain-stem auditory evoked potentials. *J. Neurosurg.* **57,** 341–348.

REBERT, C. S. (1980). The brain stem auditory evoked response as a tool in neurobehavioral toxicology and medicine. *Prog. Brain Res.* **54,** 458–462.

REBERT, C. S., HOUGHTON, P. W., HOWD, R. A., AND PRYOR, G. T. (1982). Effects of hexane on the brainstem auditory response and caudal nerve action potential. *Neurobehav. Toxicol. Teratol.* **4,** 79–85.

REBERT, C. S., PRYOR, G. T., EVANS, M. J., AND FRICK, M. S. Effects of vincristine, maytansine and cis-platinum on behavioral, electrophysiologic and histologic indicies of neurotoxicity in the rat. In preparation.

REBERT, C. S., AND SORENSON, S. S. (1983). Concentration-related effects of hexane on evoked responses from brain and peripheral nerve of the rat. *Neurobehav. Toxicol. Teratol.* **5,** 69–76.

REBERT, C. S., SORENSON, S. S., HOWD, R. A., AND PRYOR, G. T. (1983). Toluene-induced hearing loss in rats evidenced by the brainstem auditory-evoked response. *Neurobehav. Toxicol. Teratol.* **5,** 59–62.

REITER, L. W., HEAVNOR, G. B., DEAN, K. F., AND RUPPERT, P. H. (1981). Developmental and behavioral effects of early postnatal exposure to triethyltin in rats. *Neurobehav. Toxicol. Teratol.* **3,** 285–293.

REITER, L. W., RUPPERT, P. H., AND DEAN, K. F. (1983). Trimethyltin (TMT) disrupts acoustic startle responding in adult rats. *Toxicologist* **3,** 168.

SOKOL, S. (1980). Visual evoked potentials. In *Electrodiagnosis in Clinical Neurology* (M. J. Aminoff, ed.), pp. 348–369. Churchill Livingstone, New York.

STRELETZ, L. J., BAE, S. H., ROESHMAN, R. M., SCHATZ, N. J., AND SAVINO, P. J. (1981). Visual evoked potentials in occipital lobe lesions. *Arch. Neurol.* **38,** 80–85.

TOWE, A. L., AND HARDING, G. W. (1970). Extracellular microelectrode sampling bias. *Exp. Neurol.* **29,** 366–381.

WILSON, W. B., AND KEYSER, R. B. (1980). Comparison of the pattern and diffuse-light visual evoked responses in definite multiple sclerosis. *Arch. Neurol.* **37,** 30–34.

WINNEKE, G. (1979). Modification of visual evoked potentials in rats after long-term blood lead elevation. *Act. Nerv. Super.* **21,** 282–284.

WONG, P. K. H., LOMBROSO, C. T., AND MATSUMIYA, Y. (1982). Somatosensory evoked potentials: Variability analysis in unilateral hemispheric disease. *Electroencephalogr. Clin. Neurophysiol.* **54,** 266–274.

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